is requested and believed to be in order.

Claims 1-10 and 12-24 are pending. Claim 1 has been amended to include the entire phrase "wherein the composition, when administered with the adjuvant, elicits an anti-tumor response, and comprises a maximum of 7. 5×10^6 cells or cell equivalents extract per dose.", including a period at the end of the claim instead of a comma.

The Examiner has objected to the specification because it lacks a brief description of the figures. The Examiner further points out that applicant has made no amendment or arguments to refute this objection.

This objection leaves applicant confused. The figures in this application are described beginning at page 7, line 21 to page 10, line 12. Each of the 18 figures in the application is described.

The Examiner further contends that there must be a description for each A, B, etc. element in the figures. Figure 11 consists of parts A and B. A description of Figure 11A is found on page 9, lines 19-20, and Figure 11B on page 9, lines 20-22. Figure 14 consists of parts A and B. Figure 14A is briefly described on page 9, lines 29-31, and Figure 14B at line 31-32. Figure 15 consists of Figure 15A and 15B. Figure 15A is described at page 10, lines 2-4, and Figure 15B on line 4. Finally, Figure 18 consists of parts A and B. Because parts A and B show the same thing, albeit at different magnification, they are described together and on page 10, lines 11-12; A and B are specifically explained and distinguished on line 12.

It is noted that the descriptions were in some instances inserted by hand. As the declaration was signed after filing the application, these holographic changes are acceptable and should be regarded as part of the application as filed. In any event, confusion is completely dispelled because the parts A and B may have been presented as parts 1 and 2 (see, for example, the description of Figure 15 at page 10, lines 2 and 4).

In view of the foregoing remarks, applicant submit that the Examiner's objection is in error and should be withdrawn.

NON-OBVIOUS OF THE CLAIMED INVENTION

The Examiner has maintained the rejection of claims 1-23 [*sic*, 1-10 and 12-24] under the judicially created Doctrine of Double Patenting and as obvious under 35 U.S.C. §103(a). Because the basis for the rejections turns on the same references, applicants have considered them together. The Examiner has also replied to applicant's prior response in a single argument.

The thrust of the Examiner's argument is that it is routine in the art to modify immunization regimens to optimize vaccine efficacy. Thus, the Examiner has asserted that the Elliot reference, which describes weakly booster injections of an isolated tumor antigen to elicit antigen specific immunity.

Simply put, there is no objective basis to modify the teachings of Berd, which explicitly require monthly administration of a haptenized tumor cell vaccine with

an adjuvant, specifically BCG, by increasing the rate of administration to weekly. The Examiner contends that such modifications would be routine "optimization". Neither reference suggests that modifying either administration protocol will in any way lead to "optimization". Accordingly, the references are facially defective in establishing *prima facie* obviousness.

The story by no means ends with this argument, though it ought. The specification further establishes that modifying the administration regimen dramatically affects the immune response. The Examiner's attention is directed specifically to Example 15 at pages 52-53. The Example reports four different dosage schedules as set forth in the following table:

Schedule	Administration	DTH response [1]
A	Every 4 weeks, total of 8 doses of DNP-modified vaccine. Presensitization to hapten.	45% (20/44 pts.)
B	Every week, total of 6 doses of DNP-modified vaccine and 6 doses of non-haptenized vaccines (alternating). Presensitization to hapten.	11% (3/27 pts.)
C	Every week, total of 12 doses of DNP-modified vaccine. Presensitization to hapten.	18% (4/22 pts.)
D	Every week, total of 6 doses of DNP-modified vaccines. NO presensitization to hapten.	59% (16/27 pts.)

[1] To autologous, unmodified, melanoma cells.

The data show that weekly administration was clearly more effective than monthly administration, yielding 59% DTH response versus 45% DTH response.

The inventor of this application, Dr. David Berd, has provided in the accompanying Rule 132 Declaration an explanation of the unexpected features and advantages of this invention. Dr. Berd further points out the 28 day cycle described in the Berd reference was necessary to avoid administering cyclophosphomide at a more frequent basis than monthly. The Examiner will note that cyclophosphomide is immuno-suppressive. Administered at the correct time point, it inhibits a suppressive immune response and permits a protective immune response against the haptenized tumor cells, which translates into an anti-tumor immune response. A key change necessary to achieve the present invention was to omit cyclophosphomide treatment prior to each vaccine administration, thus permitting administration as frequently as weekly. Cyclophosphamide could not be administered prior to vaccine administration on a weekly basis, and nothing in the prior art suggested that this agent could be omitted with improved results (see Berd Declaration, ¶4). In particular, Examiner will note that there is nothing in Elliot to suggest this modification. Indeed, the unexpected discovery that one could omit cyclophosphomide treatment prior to each vaccine and achieve superior results underlies this invention, and this result was not predictable (Berd Declaration, ¶4).

Additional research by Dr. Berd has helped to illustrate an explanation for

the apparent difference in results between Groups C and D in Example 15. Like D, patients in Group C received weekly doses of hapten modified vaccine, for a total of 12 doses. These patients were presensitized to hapten. The poor results with the group who received 12 doses are apparently consequence of not receiving a priming dose that Dr. Berd has subsequently discovered significantly inhances the immune response (the discovery is the subject of a later-filed patent application) (Berd Declaration, ¶15). These results clearly demonstrate the unpredictability of modifications to dosage regimens. In short, there is no way to predict that any change, such as modifying the Berd protocol to change from administration of the vaccine every four weeks to every week would result in "optimization". As discussed above, the contrary result was to be expected (See Berd Declaration, ¶6). Accordingly, the discovery that weekly administration of a haptenized tumor vaccine was as, or more, effective than the 28 day cycle of administration was unpredictable.

In view of the foregoing remarks, and the expert statements of Dr. Berd, it is clear that the Examiner's basis for rejecting the claims as obvious, whether under 103(a) or for obviousness-type double patenting, fails. The references do not contain any objective teaching that permits their combination. One of ordinary skill in the art would lack any reasonable expectation of successively achieving "optimization" of the immune response by modifying the Berd vaccine as proposed by the Examiner. On the contrary, the only reasonable expectation given the state of the art and the affirmative teachings of the references would be of failure. Absent a reasonable expectation of

success, obviousness does not apply. *In re O'Farrell*, 7 USPQ 2d 1673 (Fed. Cir. 1988). Furthermore, the suggestion to combine these references and the reasonable expectation of success must be founded in the prior art and not in applicant's disclosure. *In re Vaeck*, 20 USPQ 2d 1438 (Fed. Cir. 1991). Berd discloses administration of cyclosphosplamide prior to each dose, precluding weekly administration of the vaccine; Elliott has nothing to do with tumor cell vaccines or treating patients to inhibit tumor-specific immune suppression. The objective teachings of the references taken as a whole defy a reasonable expectation of success. Given the objective teachings of the references, and the understanding of one of ordinary skill in the art at the time the invention was made, which has been established in Dr. Berd's declaration (Berd paragraph 4), it is clear that the Examiner could only arrive at this rejection from the hindsight gained from the instant application. Reliance on hindsight to arrive at a determination of obviousness, however, is not permissible. *In re Fritch*, 23 USPQ 2d 1780, 1784 (Fed. Cir. 1992).

In view of the foregoing remarks, applicant submit that the Examiner's rejections for obviousness are in error and should be withdrawn.

PRIOR ART REFERENCES

Exhibits 3, 4, and 5 to the Berd declaration relate to references published less than one year prior to filing this application. These references may teach certain aspects of the invention (references 4 and 5 of record were considered by the

Examiner and not determined relevant). The Berd declaration establishes that the only Dr. Berd made an inventive contribution to any subject matter disclosed in these references and claimed in this invention. Accordingly, these references are not prior art under 35 U.S.C. §102(a).[1]

Applicant submit herewith Form PTO 1449 (list of references cited). The Examiner is requested to initial and return this form to show that these references have been considered.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of this application, and withdrawal of finality of the final Office Action in accordance with the rules for a Request for Continued Examination. The claims are believed to be in condition for allowance. If the Examiner has any

[1] These references, even if available as prior art, neither anticipate nor render obvious the claimed invention.

further questions, she is invited to contact the undersigned by telephone. Allowance of the claims is earnestly solicited.

Respectfully submitted,

Dated: June 12, 2001

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PATENT TRADEMARK OFFICE

Docket No: 1225/1E251US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: David Berd

Serial No.: 09/304,859 Art Unit: 1642

Confirmation No.:

Filed: May 4, 1999 Examiner: J. Hunt

For: COMPOSITION COMPRISING TUMOR CELL AND EXTRACTS AND METHOD OF USING THEREOF

- -

MARK-UP FOR AMENDMENT UNDER 37 C.F.R. §1.111

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

Sir:

1. (Twice Amended) A method for inducing an anti-tumor response in a mammalian patient suffering from a tumor, which method comprises

administering to said patient a composition comprising a tumor cell or tumor cell extract

with an adjuvant, wherein the tumor cell or tumor cell extract is:

(i) conjugated to a hapten;

(ii) of the same tumor type as the patient's tumor;

(iii) not allogeneic to said patient, and

(iv) incapable of growing in the body of the patient after injection; and repeating said administration at weekly intervals,

wherein the composition, when administered with the adjuvant, elicits an anti-tumor response, and comprises a maximum of 7.5×10^6 cells or cell equivalents extract per dose.

Return of this card properly stamped, will acknowledge receipt of: NEW US PATENT APPLICATION: SPECIFICATION (32 pgs), 24 CLMS & ABSTRACT (5 pgs); UNEXECUTED DECL.(3 pgs); FORMAL DWG (1 page, FIG.1); TRANSMITTAL LTR

t of:

Applicant : David BERD
Serial No. :
Filed :
For : **LOW DOSE HAPTENIZED TUMOR CELL AND TUMOR CELL EXTRACT IMMUNOTHERAPY**

Attorney : Paul F. Fehlner, Ph.D.
File No. : 1225/1G584US2 EL706720089US

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